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| APPLICATION NO.   | FILING DATE | FIRST NAMED INVENTOR | ATTORNEY DOCKET NO. | CONFIRMATION NO.    |  |  |
|---|-------------|----------------------|---------------------|---------------------|--|--|
| 10/696,016  | 10/29/2003  | Ralph A. Casale      | BP-0206C1           | 7084                |  |  |
| 23544   | 7590        | 03/04/2009           | EXAMINER            |                     |  |  |
| Applied Biosystems<br>Mila Kasan<br>850 Lincoln Center Drive<br>Foster City, CA 94404 |             |                      |                     | LUNDGREN, JEFFREY S |  |  |
| ART UNIT  |             | PAPER NUMBER         |                     |                     |  |  |
| 1639  |             |                      |                     |                     |  |  |
| MAIL DATE   |             | DELIVERY MODE        |                     |                     |  |  |
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**Please find below and/or attached an Office communication concerning this application or proceeding.**

The time period for reply, if any, is set in the attached communication.

|                              |                        |                     |  |
|------------------------------|------------------------|---------------------|--|
| <b>Office Action Summary</b> | <b>Application No.</b> | <b>Applicant(s)</b> |  |
|                              | 10/696,016             | CASALE ET AL.       |  |
|                              | <b>Examiner</b>        | <b>Art Unit</b>     |  |
|                              | JEFFREY S. LUNDGREN    | 1639                |  |

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

#### Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

#### Status

- 1) Responsive to communication(s) filed on 11 August 2008.  
 2a) This action is **FINAL**.                    2b) This action is non-final.  
 3) Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

#### Disposition of Claims

- 4) Claim(s) 28,75-86 and 97-109 is/are pending in the application.  
 4a) Of the above claim(s) 78,79,81,85,86,101,102,104,108 and 109 is/are withdrawn from consideration.  
 5) Claim(s) \_\_\_\_\_ is/are allowed.  
 6) Claim(s) 28, 75-77, 80, 82-84, 97-100, 103 and 105-107 is/are rejected.  
 7) Claim(s) \_\_\_\_\_ is/are objected to.  
 8) Claim(s) \_\_\_\_\_ are subject to restriction and/or election requirement.

#### Application Papers

- 9) The specification is objected to by the Examiner.  
 10) The drawing(s) filed on \_\_\_\_\_ is/are: a) accepted or b) objected to by the Examiner.  
     Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).  
     Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).  
 11) The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

#### Priority under 35 U.S.C. § 119

- 12) Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).  
 a) All    b) Some \* c) None of:  
 1. Certified copies of the priority documents have been received.  
 2. Certified copies of the priority documents have been received in Application No. \_\_\_\_\_.  
 3. Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

\* See the attached detailed Office action for a list of the certified copies not received.

#### Attachment(s)

- |   |   |
|---|---|
| 1) <input type="checkbox"/> Notice of References Cited (PTO-892)  | 4) <input type="checkbox"/> Interview Summary (PTO-413)           |
| 2) <input type="checkbox"/> Notice of Draftsperson's Patent Drawing Review (PTO-948)  | Paper No(s)/Mail Date. _____ .                                    |
| 3) <input checked="" type="checkbox"/> Information Disclosure Statement(s) (PTO/SB/08)<br>Paper No(s)/Mail Date <u>4/9/08</u> . | 5) <input type="checkbox"/> Notice of Informal Patent Application |
|   | 6) <input type="checkbox"/> Other: _____                          |

## **DETAILED ACTION**

### ***Status of the Claims***

In response to the Restriction Requirement mailed on July 11, 2008, Applicants have elected the invention of Group I, claims 28, 75-86 and 97-109, without traverse.

Claims 28, 75-86 and 97-109 are pending in the instant application; claims 78, 79, 81, 85, 86, 101, 102, 104, 108 and 109, are withdrawn as being directed to non-elected species subject to the Restriction Requirement mailed on June 9, 2006; claims 28, 75-77, 80, 82-84, 97-100, 103 and 105-107 are the subject of the Office Action below.

### ***Information Disclosure Statement***

The information disclosure statement (IDS) submitted on April 9, 2008, has been considered by the Examiner. The submission is in compliance with the provisions of 37 CFR § 1.97. Enclosed with this Office Action is a return copy of the Form PTO-1449 with the Examiner's initials and signature indicating those references that have been considered.

### ***Objection to the Abstract Under 37 C.F.R. § 1.72***

The objection to the abstract is withdrawn in view of Applicants' amendment.

### ***Claim Rejections - 35 USC § 103***

The following is a quotation of 35 U.S.C. § 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

(a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negated by the manner in which the invention was made.

The factual inquiries set forth in *Graham v. John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. § 103(a) are summarized as follows:

1. Determining the scope and contents of the prior art.
2. Ascertaining the differences between the prior art and the claims at issue.
3. Resolving the level of ordinary skill in the pertinent art.

4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

Claims 28, 77, 80, 82-84, 97, 100, 103 and 105-107, are obvious over Breipohl, Kovacs, Thomson and Koch:

Claims 28, 77, 80, 82-84, 97, 100, 103 and 105-107 are rejected under 35 U.S.C. § 103(a) as being unpatentable over Breipohl *et al.*, U.S. Patent No. 6,121,418, issued on September 19, 2000; in view of Kovacs *et al.*, Fourth International Electronic Conference on Synthetic Organic Chemistry (ECSOC-4), [www.mdpi.org/ecsoc-4.htm](http://www.mdpi.org/ecsoc-4.htm), September 1, 2000; Thomson *et al.*, *Tetrahedron* 51:6179-6194 (1995), and Koch *et al.*, *J. Peptide Res.* 49:80-88 (1997), and optionally Grubler *et al.*, *Innovation Perspect. Solid Phase Synth. Collect. Pap., Int. Symp., 3rd Mayflower Worldwide Ltd.*, pages 517-520 (1993); Bollhagen *et al.*, *J. Chem. Soc., Chem. Commun.*, pages 2559-2560 (1994), Rudolph *et al.*, U.S. Patent No. 6,982,315, issued on January 3, 2006; and Barlos *et al.*, *Tetrahedron Letters*, 30(30):3943-3946 (1989) (English translation of the German document).

Claim 28 is directed to a method for forming a support bound PNA dimer, the method comprising: a) coupling a first PNA monomer to a sterically hindered solid support comprising a sterically hindered acid forming cleavable linker wherein the PNA monomer comprises a N-terminal amine base labile protecting group; b) optionally washing the solid support to remove excess first PNA monomer; c) treating the solid support for a period of about 1 to about 2 minutes with a deprotection reagent that substantially removes the base labile N-terminal amine protecting group from the support; d) washing the solid support to remove the deprotection reagent; and e) coupling a second PNA monomer to the N-terminal amine of the first PNA monomer after performing steps (c) and (d). Claim 97 is similar.

Breipohl teaches a method for synthesizing PNA oligomers on a solid support, wherein the PNA monomer comprises a N-terminal amine base labile protecting group, and the solid support is a rink-type resin (col. 5, lines 25-26, in reference to prior art disclosure H. Rink, *Tetrahedron Letters* 1987, 3787-3790).<sup>1</sup> The group in Rink meet the limitations of the sterically

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<sup>1</sup> Since Rink is effectively incorporated by reference, in particular the teachings as it pertains to PNA suitable resin supports, Breipohl is treated as teaching these limitations. See, *Advanced Display Systems Inc. v. Kent State University*, 54 USPQ2d 1673 at 1679 (Fed. Cir. 2000) – “Incorporation by reference provides a method for

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hindered acid forming cleavable linker, and the trityl chloride resin of claim 82-84 and 105-107 (regarding claims 84 and 107, Breipohl's commercially available resin, such as the Rink resin, provides greater than 0.08 mmol per gram). Breipohl also teaches treating the solid support with deprotection reagents:

"Examples of reagents for eliminating the base-labile amino protecting group PG are a solution of piperidine, morpholine, hydrazine or 1,8-diazabicyclo[5.4.0]undec-7-ene (**DBU**) in diisopropylformamide, N-methylpyrrolidinone (**NMP**), acetonitrile (ACN) or dichloromethane (DCM); the use of 20% piperidine in DMF or N-methylpyrrolidinone and also of a mixture of 2% **DBU** and 2% piperidine in DMF or 0.1M DBU in DMF or 0.1M DBU in dichloromethane is particularly preferred for the Fmoc, Dnpeoc and Bnpeoc protecting groups."

Breipohl, col. 7, lines 22-33 (emphasis added). Accordingly, the limitations of claims 80 and 103 are taught. Breipohl teaches using various protecting groups:

Protecting groups which are compatible with the base-labile amino protecting group PG, such as, for example, protecting groups, which are labile to weak or medium strength acids, of the urethane type, such as tertbutyloxycarbonyl (Boc), 4-methoxybenzyloxycarbonyl (Moz) or 3,5-dimethoxyphenyl-2-propyl-2-oxycarbonyl (Ddz), or of the trityl type, such as triphenylmethyl (Trt), (4-methoxyphenyl)diphenylmethyl (Mmt), (4-methylphenyl)-diphenylmethyl (Mtt), di-(4-methoxyphenyl)phenylmethyl (Dmt) or 9-(9-phenyl)xanthenyl (pixyl) are used for protecting the exocyclic amino function in the nucleotide bases B' which are protected in their exocyclic amino function. The use of butyloxycarbonyl (Boc), triphenylmethyl (Trt), (4-methoxyphenyl)diphenylmethyl (Mmt), (4-methylphenyl)diphenylmethyl (Mtt) or di-(4-methoxyphenyl)phenylmethyl (Dmt) is particularly preferred, with Trt, Mtt, Mmt and Dmt surprisingly effecting a marked improvement in the solubility of the monomers. The use of (4-methoxyphenyl)diphenylmethyl (Mmt) is very particularly preferred."

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integrating material from various documents into a host document --a patent or printed publication in an anticipation determination-- by citing such material in a manner that makes clear that the material is effectively part of the host document as if it were explicitly contained therein. *See General Elec. Co. v. Brenner*, 407 F.2d 1258, 1261-62, 159 USPQ 335, 337 (D.C. Cir. 1968); *In re Lund*, 376 F.2d 982, 989, 153 USPQ 625, 631 (CCPA 1967). To incorporate material by reference, the host document must identify with detailed particularity what specific material it incorporates and clearly indicate where that material is found in the various documents. *See In re Seversky*, 474 F.2d 671, 674, 177 USPQ 144, 146 (CCPA 1973) (providing that incorporation by reference requires a statement "clearly identifying the subject matter which [page 1680] is incorporated and where it is to be found"); *In re Saunders*, 444 F.2d 599, 602-03, 170 USPQ 213, 216-17 (CCPA 1971) (reasoning that a rejection for anticipation is appropriate only if one reference "expressly incorporates a particular part" of another reference).

Breipohl, col. 7, lines 3-23.

As in claims 77 and 100, Breipohl also teaches a number of base labile protecting groups, such as Fmoc and Bnpeoc (Breipohl, col. 6, lines 1-15). As in claims 87-89, Breipohl also teaches benzyloxycarbonyl (*i.e.*, Bhoc or Z; col. 12, line 63), and teaches t-boc (*i.e.*, Boc), Mmt and Fmoc, and suggests that these groups may be used in many combinations for protection. As in claims 76 and 99, Breipohl suggests the nucleobases adenine and cytosine.

Although Breipohl teaches the methods for forming PNA oligomers on resins using base-labile protecting groups, Breipohl does not explicitly state that a period of about 1 to about 2 minutes is the time for deprotection to avoid cyclization side reactions.

Kovacs teaches a method of synthesizing PNA oligomers on a solid phase. As part of the method, Kovacs teaches the removal of the N-terminal amine protecting group in about five minutes (see Scheme 2). Kovacs teaches coupling a first PNA monomer to a solid support (NovaSyn hydroxy-Tentagel resin) comprising an acid forming cleavable linker, wherein the PNA monomer comprises base labile N-terminal protecting groups (*i.e.*, Boc/Z and Fmoc/Z).

Thomson teaches PNA oligomer synthesis on resins. Thompson teaches a deprotection step that is carried out at 3 x 5 minutes.

Although Koch is primarily focused on the use of acid-labile protecting groups (such as that of previous claim 41), Koch directly acknowledges what is known in the art by those who practice using base-labile PNA amino protecting groups (as in claim 28):

“It is now apparent that the chemical structure of the PNA monomer sets certain limits to the choice of optimal oligomerization strategy. ***Basic media promotes side reactions of PNA oligomers*** with liberated ***primary amines must be treated in the shortest possible time with a minimal amount of base.***”

Koch, page 80, col. 2, first full paragraph (emphasis added).

Gruebler teaches a solid support composition comprising a sterically hindered linker that attaches the amino acid groups to a resin. Grubler states that:

“Due to the extreme steric hindrance of the trityl group of the above resin, we expect to overcome [the diketopiperazine] side reaction using TentaGel S-Trt-Pro-Fmoc for the solid phase synthesis of a recently described peptide...”

The trityl group of Grubler meets the limitations of the sterically hindered acid-forming cleavable linker. Each of Bollhagen and Barlos are similar to Grubler, and further support the understanding that sterically hindered resin linkers such as trityl when linked to amino acid bond-based oligomers resist diketopiperazine side reactions that take place under basic conditions. Rudolph is similar (see Example 7).

One of ordinary skill in the art would have had a reasonable expectation of success in arriving at the invention as claimed because each of Breipohl, Kovacs, Thomson and Koch are directed to PNA based oligomer formation on solid phases. Koch specifically notes the side reactions that occur using PNA oligomers, and in view of Kovacs and Thompson, those of skill in the art recognize that there are varying reaction conditions for optimizing synthesis of a PNA oligomer (see Koch, page 81, col. 1, lines 1-20; and page 81, col. 2, lines 10-15, wherein 3 minutes are taught; see Thomson on page 6192, last paragraph). It is noted that it is also well known that the sterically hindered trityl groups also increase the loading efficiency of amide backbone bonded oligomers. Therefore, the invention as a whole was *prima facie* obvious at the time it was invented.

Claims 28, 75-77, 80, 82-84, 97-100, 103 and 105-107 are obvious over Breipohl, Kovacs, Thomson, Koch and Seitz:

Claims 28, 75-77, 80, 82-84, 97-100, 103 and 105-107 are rejected under 35 U.S.C. § 103(a) as being unpatentable over Breipohl *et al.*, U.S. Patent No. 6,121,418, issued on September 19, 2000; in view of Kovacs *et al.*, Fourth International Electronic Conference on Synthetic Organic Chemistry (ECSOC-4), [www.mdpi.org/ecsoc-4.htm](http://www.mdpi.org/ecsoc-4.htm), September 1, 2000; Thomson *et al.*, *Tetrahedron* 51:6179-6194 (1995), and Koch *et al.*, *J. Peptide Res.* 49:80-88 (1997), Grubler *et al.*, *Innovation Perspect. Solid Phase Synth. Collect. Pap., Int. Symp., 3rd Mayflower Worldwide Ltd.*, pages 517-520 (1993); Bollhagen *et al.*, *J. Chem. Soc., Chem. Commun.*, pages 2559-2560 (1994), Rudolph *et al.*, U.S. Patent No. 6,982,315, issued on January 3, 2006; and Barlos *et al.*, *Tetrahedron Letters*, 30(30):3943-3946 (1989) (English translation of the German document); in further view of Seitz *et. al.*, *J. Org. Chem.*, 62:813-826 (1997).

The limitations of the previously cited claims and the corresponding teachings of Breipohl, Kovacs, Thomson and Koch are found in the rejection above, and hereby incorporated into the instant rejection by reference.

Although Breipohl, Kovacs, Thomson and Koch, are each directed to base labile protecting groups for oligomeric synthesis, none explicitly teach the Fmoc(Bhoc) protecting groups as set forth in claims 75 and 98.

As in claim 28, Seitz teaches a method for forming a support bound PNA oligomer, including dimers. In scheme 4, and description thereof, Seitz teaches coupling a first PNA monomer to a sterically hindered solid support comprising a sterically hindered acid forming cleavable linker (HYCRON resin; *i.e.*, the double bond is sterically hindered, and upon ozonolysis and peroxide treatment, alkene groups form an organic acid group), wherein the PNA monomer comprises a N-terminal protecting group. Subsequent PNA monomers are added sequentially to the resin to form a surface attached PNA oligomer. As in claims 75 and 77, and claims 98 and 99, Seitz teaches Fmoc/Bhoc protected PNA oligomer synthesis, wherein the nucleobase protecting group is Fmoc (page 4163, paragraph positioned directly above Scheme 4, last sentence); Seitz also teaches a PNA with a cytosine nucleobase.

One of ordinary skill in the art would have had a reasonable expectation of success in arriving at the invention as claimed because each of Breipohl, Kovacs, Thomson, Koch and Seitz are directed to PNA based oligomer formation on solid phases. Koch specifically notes the side reactions that occur using PNA oligomers, and in view of Kovacs and Thompson, those of skill in the art recognize that there are varying reaction conditions for optimizing synthesis of a PNA oligomer (see Koch, page 81, col. 1, lines 1-20; and page 81, col. 2, lines 10-15, wherein 3 minutes are taught; see Thomson on page 6192, last paragraph), and Seitz explains the advantages of the Fmoc/Bhoc protecting group strategy. Therefore, the invention as a whole was *prima facie* obvious at the time it was invented.

### ***Conclusions***

No claim is allowable.

Any inquiry concerning this communication or earlier communications from the Examiner should be directed to Jeff Lundgren whose telephone number is 571-272-5541. The Examiner can normally be reached from 7:00 AM to 5:30 PM.

If attempts to reach the Examiner by telephone are unsuccessful, the Examiner's supervisor, Christopher Low, can be reached on 571-272-0951. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see <http://pair-direct.uspto.gov>. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

/Jeffrey S. Lundgren/  
Patent Examiner, Art Unit 1639